REMARKS

Status of the claims

Upon entry of these remarks, claims 16-28, 30, 31 and 139-155 will be pending in this application. Claims 140-155 have been added. Claims 1, 29, 32, 48, 63, 78, 103 and 121 have been cancelled herein. Cumulatively, claims 1-15, 29 and 32-138 have been cancelled. Applicants reserve the right to pursue the subject matter of the cancelled claims in one or more divisional applications.

Substitute Declaration

The Examiner required a Supplemental Declaration in compliance with 37 C.F.R. § 1.67 because the Declaration submitted with this application (which was a copy from parent application NO. 09/840,989 filed April 25, 2001) contained non-initialed and or non-dated alterations. Applicants have reviewed the declaration from the parent application and have identified two instances where the signing inventors made handwritten changes to the Declaration, but failed to date and initial the changes. Specifically, inventor Ke-Zhou Zhang crossed out the typed citizenship indicated as "FI" (Finland) and hand wrote in "Chinese" and inventor Leif C. Andersson crossed out the typed citizenship indicated as "SE" (Sweden) and hand wrote in "FI" (Finland).

In response, Applicants submit herewith a Supplemental Declaration in compliance with 37 C.F.R. 1.67 that specifically identifies the present application by application and filing number. On the date of this filing, Applicants are also filing a Supplemental Declaration in compliance with 37 C.F.R. 1.67 in parent application Number 09/840,989 filed April 25, 2001.

Amendments to the Specification

The Examiner objected to the specification because paragraphs [0114] (and [0115]) had text "blacked out"; because paragraph [0115] was missing; and because spaces were missing in the references to certain International Patent Application Publications in paragraphs [0307], [536] and [0539].

Original paragraphs [0114] and [0115] inadvertently contained highlighted text which made certain of the text appear blacked out. Applicants present above replacement paragraphs [0114] and [0115] in which the highlighting has been removed. No other amendment has been made to

these paragraphs. Applicant does not see that paragraph [0115] is missing, but rather, that the paragraph number for paragraph [0115] was highlighted.

Applicants have also inserted the missing spaces in the references to certain International Patent Application Publications in paragraphs [0407] and [0536] and [0539] as requested.

Applicants believe these amendments overcome the Examiner's objections to the specification.

Amendments to the claims

Claim 16 has been amended to recite a "mammalian cell." Claim 16 has also been amended to add new subpart (a) to include the use of the full length polypeptide of SEQ ID NO:2 in the claimed method. Lastly, claim 16 and claim 24 have been amended to delete the phrase "has stanniocalcin biological activity" and replace it with "is capable of increasing resistance of a mammalian cell to hypoxic stress." Support for these amendments may be found, for example in paragraph [0349] and Example 1.

Claim 140, dependent from claim 16 has been added to create a dependent claim directed to Markush member (h) of claim 16.

The spelling of "heterologous" has been corrected in claims 25 and 26.

Original claim 29 has been rewritten in independent form as new claim 141 and dependent claims 142-155 which mirror original claims 17-23, 141, 24-28 and 30, respectively have been added.

Applicants submit that no new matter has been added by way of these amendments and respectfully request entry of these amendments into the record.

Rejection of claims 16-31 and 139 under 35 U.S.C. 112, first paragraph - enablement

The Examiner has rejected claims 16-31 and 139 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. More specifically, the Examiner states that "the specification while being enabling for a method of increasing resistance of a cell to hypoxic stress, comprising contacting the cell with a stanniocalcin polypeptide comprising the amino acid sequence of SEQ ID NO:2, does not reasonably provide enablement for fragments, sequence variants, muteins of SEQ ID NO:2."

The Examiner further outlines the state of the art by reference to three scientific articles, Verbost and Fenwick (May 1995)[1] and Yoshiko *et al.*, (May 1996)[2] and Stern *et al.* (1991)[3]. The Examiner cited Verbost and Fenwick to show that different fragments of stanniocalcins from bony fish have different effects, and that fragments of stanniocalcin from bony fish may have different effects based dependent upon the animal model in which they are tested. Yoshiko *et al.* study the effects of a single stanniocalcin peptide fragment from chum salmon on the metabolism of mammalian bone cell and states that this STC fragment has "diverse effects on mammalian bone." Lastly, the Examiner cites Stern *et al.* apparently for the purpose of demonstrating that a salmon stanniocalcin peptide "does not have the same effects in mammals as it does in fish." (See end of paragraph 12 in the Office Action mailed August 17, 2004.)

The Examiner asserts that:

> due to the large quantity of experimentation necessary to identify all the applicable fragments of SEQ ID NO:2, the lack of direction/guidance presented in the specification regarding synthesizing, screening and evaluating all applicable fragments of SEQ ID NO:2, the absence of working examples directed known fragments of SEQ ID NO:2, the complex nature of the invention, the unpredictability of the effects of fragments of SEQ ID NO:2 on cells and/or patients and the breadth of the claims which fail to recite limitations for what constitutes an applicable fragments of SEQ ID NO:2, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. (See paragraph 14 of the Office Action mailed August 17, 2004)

Applicants respectfully disagree:

Applicants remind the Examiner that the enablement requirement of 35 U.S.C. § 112, first paragraph requires nothing more than objective enablement. A specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of § 112, unless there is reason to doubt the objective truth or accuracy of the statements relied upon therein for enabling support. *Staehelin v Secher*, 24 USPQ2d 1513, 1516 (B.P.A.I. 1992), *In re Marzocchi*, 169 USPQ 367 (C.C.P.A. 1971); *In re Brana* 34 USPQ2d 1437, 1441 (Fed. Cir. 1995).

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[1] Cited by Examiner as reference U on Form PTO-892 mailed with the Office Action of August 17, 2004.
[2] Cited by Examiner as reference V on Form PTO-892 mailed with the Office Action of August 17, 2004.
[3] Cited by Applicants as reference N on Revised Form PTO-/SB/08A submitted July 9, 2003, the initialed copy of which was returned to Applicants with the Office Action of August 17, 2004.

The Examiner is of the opinion that a "large quantity of experimentation" would be necessary to identify an stanniocalcin fragments and/or variants that fall within the scope of the rejected claims. However, a large quantity of routine experimentation is not sufficient to render claims non-enabled. Section 2164.06 of the M.P.E.P (8th edition), states that

> [t]he quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Furthermore, in *In re Wands* 858 F.2d 731, 740, the Federal Circuit acknowledged that it is routine (i.e., not undue) experimentation for one of skill in the monoclonal antibody art to screen through hundreds of hybridomas in pursuit of hybridomas with the desired characteristics. *Id.* at 738 and 740. Thus, the fact that screening for stanniocalcin fragments and/or variants that are capable of protecting a mammalian cell from hypoxic stress will require testing stanniocalcin fragments and/or variants that are not capable of protecting a mammalian cell from hypoxic stress, does not preclude the enablement of stanniocalcin fragments and/or variants that do.

Applicants also remind the Examiner that the law does not require that Applicants forecast the results of an experiment before it is done. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 537 F.2d 498 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, *with reasonable certainty before performing the reaction* whether the claimed product will be obtained, . . . then *all* "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is *uncertain.* Such a proposition is contrary to the basic policy of the Patent Act.

Id. at 503 (emphasis in the original). As Judge Rich explained in *In re Vaeck*, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991), the statutory enablement requirement is satisfied if the specification "adequately guides the worker to *determine*, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility" (emphasis provided). Since the disclosed or otherwise known methods of making and screening polypeptides (and fragments or variants thereof) may be used to make and then *determine*, without undue experimentation, whether a given polypeptide encompassed by the claims is able to protect a mammalian cell from hypoxic stress, the enablement requirement is fully satisfied. *In re Wands*, 8 USPQ2d at 1404; *Ex parte Mark*, 12 USPQ2d 1904, 1906-1907 (B.P.A.I. 1989).

Applicants submit that the specification provides ample guidance for one of ordinary skill in the art to routinely make the polypeptides described in the claims and to use them in the claimed methods. For example, the specification discloses both the nucleic acid and amino acid sequences of stanniocalcin, routine cloning methods (*See, e.g.*, the specification at paragraph [0246] to [0256]), stanniocalcin activity, and biological assays including, for example, assays to determine if a polypeptide would be able to protect a mammalian cell from hypoxic stress (*See, e.g.*, the specification at Example 1).

Moreover, the skill in the art of molecular biology is high. The skilled molecular biologist, enlightened by the teaching of the present specification and armed with the knowledge available in the art at the time of filing of the earliest priority document of the present application, would be more than capable of routinely making proteins with at least 90% sequence identity with the amino acid sequence of SEQ ID NO:2 or a fragment thereof that display stanniocalcin activity as encompassed by the claims. In particular, Example 1 of the instant specification explicitly teaches an assay which could be used to measure the ability of a polypeptide to protect a cell from hypoxic stress. Thus, the skilled artisan could readily and routinely test whether a protein with at least 90% sequence identity with the amino acid sequence SEQ ID NO:2 or a fragment thereof has such activity and is useful in the claimed methods.

Moreover, Applicants submit that the Verbost and Fenwick Assay reference supports Applicants arguments. Prior to the earliest effective filing date of the present application, Verbost and Fenwick were able to make fragments of a species orthologue of the protein of SEQ

ID NO:2 and test them for biological active and determine, without undue experimentation, which fragments had activity and which did not.

In so far as the Examiner relies on the Yoshiko and Stern references, Applicants submit that these references are not dispositive of the state of the art of the claimed invention in view of the amendments made herein. Both the Yoshiko and Stern references report the results of the use of stanniocalcins from bony fish in mammalian systems. Applicants are claiming the use of a mammalian protein to contact mammalian cells. Because mammalian species are more recently diverged from one another on an evolutionary scale, it is much more likely that the function of a protein across mammalian species will be conserved compared to the use of a protein from a teleost fish in a mammalian system.

Additionally, the fact that a protein may have additional biological effects (as described for the chum salmon stanniocalcin protein fragment studied in the Yoshiko reference) would not prevent one of skill in the art from ascertaining whether a given fragment or variant of the human stanniocalcin protein described in the present application is able to protect a mammalian cell from hypoxic stress.

Finally, as regards the ability to predict the activity of a stanniocalcin polypeptide fragment and/or variant from *in vitro* studies, Applicants remind the Examiner that the only a reasonable correlation between *in vitro* and/or *in vivo* (e.g. animal model) data and a claimed method of use is required to meet the enablement standard. (see M.P.E.P., 8th edition, Revision 2, May 2004 at § 2164.02, text spanning pages 2100-187 and 2100-188). Applicants point out that in the *in vitro* test described in Example 1 utilizing Paju cells treated with $CoCl_2$ is "commonly used to mimic hypoxic insults both *in vitro* and *in vivo*." (See, specification as filed at paragraphs [0486]-[0487]). In support of this statement, Applicants submit the abstracts of two pre-filing date references (Chandel *et al.*[4] and Badr *et al.*[5]) which each state that the $CoCl_2$ treatment of cells induces the transcription of genes that are also induced during hypoxia. Paragraph [0487] further describes that overexpression of stanniocalcin in Paju cells treated with $CoCl_2$. Moreover, Example 1 further goes to demonstrate that in animal models of an ischemic brain and in a sample taken from a human patient (see, paragraphs [0490]-[0491] of the

[4] Chandel et al., (1998) Mitochondrial reactive oxygen species trigger hypoxia-induced transcription. *Proc Natl Acad Sci U.S A.* 95:11715-20.

[5] Badr et al., (1999) Glut1 and glut3 expression, but not capillary density, is increased by cobalt chloride in rat cerebrum and retina. *Brain Res Mol Brain Res.* 64:24-33.

specification as filed) that died of ischemic stroke, stanniocalcin is transiently upregulated and redistributed in neurons. This additional evidence goes to show that there is a strong correlation between the claimed method and the *in vitro* data shown in Example 1. Section 2164.02 of the M.P.E.P. specifically instructs, "if the art is such that that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." Applicants have shown that $CoCl_2$ treatment is an art accepted model of hypoxia, that stanniocalcin can protect cells from the hypoxic effects induced by CoCl2 treatment and have also shown data from animal models of brain ischemia and from a sample taken from a human patient that died of ischemic stroke that corroborates the involvement of stanniocalcin in protecting cells from hypoxia.

Applicants submit that because one of ordinary skill in the art can readily make and test the claimed stanniocalcin fragments and variants in an *in vitro* assay that is art accepted to mimic the conditions of hypoxia and to determine, without undue experimentation, which fragments and/or variants have the claimed activity of protecting a mammalian cell from hypoxic stress, the enablement requirement of 35 U.S.C. 112, first paragraph has been fully satisfied. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection of claims 16-31 and 139 under 35 U.S.C. 112, first paragraph – written description

The Examiner rejected claims 16-31 and 139 for allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention." (See, Office Action mailed August 17, 2004).

The Examiner is of the opinion "that the claims do not require that the polypeptide possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity." (See, Office Action mailed August 17, 2004 at paragraph 16).

Applicants respectfully disagree.

The test for written description is whether one skilled in the art could reasonably conclude that the inventor has possession of the claimed invention in the specification as filed, *Vas Cath v. Mahurkar,* 935 F2d 1555, 1563 19 U.S.P.Q. 2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02. The Federal Circuit recently re-emphasized the well settled principle of law that, "[t]he written descrition requirement does not require the Applicant to describe exactly the subject matter as

claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [they] invented what is claimed.'" *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 54 U.S.P.Q.2d 1227 (Fed. Cir. 2000).

Preliminarily, Applicants note that claim 16 requires the claimed stanniocalcin fragments and/or variants to have a particular structure, i.e., a sequence of amino acids that is at least 90% identical to all or a portion of SEQ ID NO:2. Moreover, Applicants have amended the claim to make what was implicit in claim 16, explicit by requiring that the claimed stanniocalcin fragments and/or variants are "capable of protecting a mammalian cell from hypoxic stress."

Additionally, as mentioned above in the section regarding enablement of the claimed invention, Applicants have written description for the claimed stanniocalcin fragments and variants. Paragraphs [0085] to [0109] describe numerous staniocalcin fragments and variants. And Example 1, as described above provides an assay that may be carried out by one of ordinary skill in the art to test the fragments and variants for the biolgical activity as encompassed by the claims, without undue experimentation.

In view of the amendments to claim 16 and the arguments made above, Applicants submit that one skilled in the art would reasonably conclude that Applicants had possession of the stanniocalcin fragments and variants on the effective filing date of the present application. Accordingly, Applicants respectfully request that the written description rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Availability of Deposited Material

Claim 16 was rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the claimed invention. More specifically, the Examiner states that "since the cDNA of claim 16(d) is essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise available to the public." (See paragraph 21 on page 11 of the Office Action mailed August 17, 2004.)

In response, Applicants note that the specification indicates that the deposit of ATCC Deposit No. 75652 was made under the Budapest Treaty. *See, e.g.,* paragraph [0031] on page 7. Applicants also point out that the correct address of the depository is also indicated in this paragraph.

Further, Applicants' representative hereby gives the following assurance by signature below:

Human Genome Sciences, Inc., the assignee of the present application, has deposited biological material under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for the Purposes of Patent Procedure with the following International Depository Authority: American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209. A deposit of a plasmid containing the cDNA referred to in claim 16(d) was made on January 25, 1994, and given ATCC Accession Number 75652. In accordance with M.P.E.P. § 2410.01 and 37 C.F.R. § 1.808, assurance is hereby given that all restrictions on the availability to the public of ATCC Accession Number Accession Number 75652 will be irrevocably removed upon the grant of a patent based on the instant application, except as permitted under 37 C.F.R. § 1.808(b). A partially redacted copy of the ATCC Deposit Receipt for Accession Number Accession Number 75652 is enclosed herewith.

As a result, Applicants submit that the Examiner's rejection of claim 16 under 35 U.S.C. § 112, first paragraph, is obviated by the above statement regarding availability of the deposited material, and Applicants respectfully request that the rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants believe that this application is now in condition for substantive examination. The Examiner is invited to call the undersigned at the phone number provided below if any further action by applicant would expedite the examination of this application.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: December 17, 2004

Respectfully submitted,

By Michele Shannon

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MJP/MS/ba

American Type Culture Collection

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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3 AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Human Genome Sciences, Inc.
Attention: Craig A. Rosen, Ph.D.
9620 Medical Center Drive, Suite 300
Rockville, MD 20850

Deposited on Behalf of: Human Genome Sciences, Inc.

Identification Reference by Depositor:	**ATCC Designation**
DNA Plasmid, HLFBE10S06	75652 PF 108

The deposits were accompanied by: __ a scientific description __ a proposed taxonomic description indicated above.

The deposits were received January 25, 1994 by this International Depository Authority and have been accepted.

AT YOUR REQUEST:

X We will inform you of requests for the strains for 30 years.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years after the date of deposit, and for a period of at least five years after the most recent request for a sample. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested February 1, 1994. On that date, the cultures were viable.

International Depository Authority: American Type Culture Collection, Rockville, Md. 20852 USA

Signature of person having authority to represent ATCC:

Bobbie A. Brandon Date: February 2, 1994

Bobbie A. Brandon, Head, ATCC Patent Depository

cc: Greg Ferraro

1: Proc Natl Acad Sci U S A. 1998 Sep 29;95(20):11715-20.

Mitochondrial reactive oxygen species trigger hypoxia-induced transcription.

Chandel NS, Maltepe E, Goldwasser E, Mathieu CE, Simon MC, Schumacker PT.

Department of Medicine, The University of Chicago, Chicago, IL 60637, USA.

Transcriptional activation of erythropoietin, glycolytic enzymes, and vascular endothelial growth factor occurs during hypoxia or in response to cobalt chloride (CoCl2) in Hep3B cells. However, neither the mechanism of cellular O2 sensing nor that of cobalt is fully understood. We tested whether mitochondria act as O2 sensors during hypoxia and whether hypoxia and cobalt activate transcription by increasing generation of reactive oxygen species (ROS). Results show (i) wild-type Hep3B cells increase ROS generation during hypoxia (1. 5% O2) or CoCl2 incubation, (ii) Hep3B cells depleted of mitochondrial DNA (rho0 cells) fail to respire, fail to activate mRNA for erythropoietin, glycolytic enzymes, or vascular endothelial growth factor during hypoxia, and fail to increase ROS generation during hypoxia; (iii) rho0 cells increase ROS generation in response to CoCl2 and retain the ability to induce expression of these genes; and (iv) the antioxidants pyrrolidine dithiocarbamate and ebselen abolish transcriptional activation of these genes during hypoxia or CoCl2 in wild-type cells, and abolish the response to CoCl2 in rho degrees cells. Thus, hypoxia activates transcription via a mitochondria-dependent signaling process involving increased ROS, whereas CoCl2 activates transcription by stimulating ROS generation via a mitochondria-independent mechanism.

PMID: 9751731 [PubMed - indexed for MEDLINE]

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1: Brain Res Mol Brain Res. 1999 Jan 22;64(1):24-33.

Glut1 and glut3 expression, but not capillary density, is increased by cobalt chloride in rat cerebrum and retina.

Badr GA, Zhang JZ, Tang J, Kern TS, Ismail-Beigi F.

Departments of Medicine and Physiology and Biophysics, and Diabetes Research Center, Case Western Reserve University, Cleveland, OH 44106-4951, USA.

Treatment of rats with cobalt chloride [Co(II)], an agent that stimulates the expression of a set of hypoxia-responsive genes, for 10-12 days resulted in 1.45- and 1.40-fold increases in the content of Glut1 mRNA and Glut1 in cerebral gray matter, respectively (P<0. 05 for both changes). The increase in Glut1 content was associated with a significant increase in the content of Glut1 staining in microvessels isolated from cerebral gray matter, and in the intensity of Glut1 in microvessels of the frontal lobe and hippocampus assessed by immunohistochemistry. The abundance of Glut3 in cerebrum of Co(II)-treated rats also increased by 1.3-fold (P<0. 05), but the increase was not associated with a change in the content of Glut3 mRNA. In retina, treatment with Co(II) resulted in 2.48- and 1.23-fold increases in the content of Glut1 mRNA and Glut1 protein, respectively (P<0.05 for both changes); similar increases in Glut1 protein expression were observed in isolated retinal microvasculature. The content of Glut3 in retina also increased 1. 5-fold in Co(II)-treated rats (P<0.05). In addition, treatment with Co(II) resulted in a significant 2.2-fold increase in the expression of VEGF in the cerebrum. However, despite the Co(II)-induced increase in Glut1 expression in cerebral and retinal microvasculature and VEGF in cerebrum, there was no increase in the capillary density in either tissue. It is concluded that a 10-12 day exposure to Co(II), presumably acting through the hypoxia-signaling pathway, results in enhanced expression of both major glucose transporters in cerebral cortex and retina, without increasing the capillary density of either tissue.

PMID: 9889305 [PubMed - indexed for MEDLINE]

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